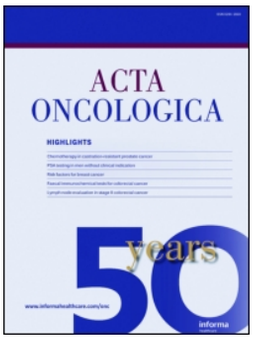

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ORIGINAL ARTICLE

Exercise prehabilitation for people with myeloma undergoing autologous stem cell transplantation: results from PERCEPT pilot randomised controlled trial

Orla McCourt[a,b], Abigail Fisher[c], Gita Ramdharry[d], Joanne Land[b,c], Anna L. Roberts[c], Neil Rabin[e] and Kwee Yong[b]

[a]Therapies & Rehabilitation, University College London Hospitals NHS Foundation Trust, London, UK; [b]Department of Haematology, UCL Cancer Institute, University College London, London, UK; [c]UCL Department of Behavioural Science and Health, University College London, London, UK; [d]Queens Square Centre for Neuromuscular Diseases, National Hospital for Neurology & Neurosurgery, UCLH NHS Trust/UCL Institute of Neurology, University College London, London, UK; [e]Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK

ABSTRACT

Background: Autologous stem cell transplant (ASCT) is first line treatment for newly diagnosed patients with myeloma but often results in functional deficits and reduced quality of life (QOL). Physically active myeloma patients have better QOL, less fatigue and reduced morbidity. This trial aimed to investigate the feasibility of a physiotherapist-led exercise intervention delivered across the continuum of the myeloma ASCT pathway at a UK centre. Initially designed and delivered as a face-to-face trial, the study protocol was adapted to virtual delivery in response to the COVID-19 pandemic.

Material and methods: A pilot randomised controlled trial of a partly supervised exercise intervention with incorporated behaviour change techniques delivered before, during and for 3 months following ASCT compared to usual care. Face-to-face delivery of the pre-ASCT supervised intervention was adapted to virtually-supervised group classes via video conferencing. Primary outcomes related to feasibility; recruitment rate, attrition and adherence. Secondary outcomes included patient reported measures of QOL (EORTC C30, FACT-BMT, EQ5D), and fatigue (FACIT-F), measures of functional capacity (six-minute walk test (6MWT), timed sit-to-stand (TSTS), hand grip strength, self-reported and objective physical activity (PA).

Results: Over 11 months 50 participants were enrolled and randomised. Overall, uptake to the study was 46%. The attrition rate was 34%, mainly related to failure to undergo ASCT. Loss of follow-up for other reasons was low. Secondary outcomes demonstrate potential for the benefit of exercise prior to, during and after ASCT with improvements in QOL, fatigue, functional capacity and PA evident on admission for ASCT and 3 months post-ASCT.

Discussion: Results indicate acceptability and feasibility of delivering exercise prehabilitation, in person and virtually within the ASCT pathway in myeloma. The effects of prehabilitation and rehabilitation provision as a component of the ASCT pathway warrants further investigation.

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KEYWORDS
Myeloma; haematopoietic stem cell transplantation; prehabilitation; rehabilitation; exercise; physiotherapy

Background

Myeloma is a haematological malignancy of the plasma cells in the bone marrow [1,2]. Incidence increases with age, with a marked increase from 55 years [3]. Although incurable, myeloma is characterised by periods of active, symptomatic disease that require intensive treatment, separated by periods of stable disease where no, or only maintenance treatment is required. Myeloma has the fastest increasing survival rate among all cancer types in the UK [4].

Autologous stem cell transplantation (ASCT) and the introduction of novel treatment agents are likely responsible for the increasing prolonged survival in myeloma [2]. ASCT is most frequently used as part of the treatment protocol for newly diagnosed patients who are considered 'fit' enough for intensive chemotherapy. Survival outcomes following ASCT have been steadily improving with 5-year survival estimated to be as high as 70% for patients receiving ASCT in more recent years [5].

ASCT in myeloma is considered less intensive than other transplantation regimens, but myeloma patients present with unique exercise and rehabilitation needs and challenges. They experience comparably more symptoms than those with other haematological cancers [6–8], with fatigue, pain, peripheral neuropathy and reduction in physical functioning most frequently reported [9]. Bone disease is a common defining feature of myeloma, prevalent in 80–90% of patients at diagnosis with 50–60% expected to develop fractures

CONTACT Orla McCourt o.mccourt@nhs.net Inpatient Therapy Office, University College Hospital, T-1/Lower Ground Floor, 235 Euston Road, London NW1 2BU, UK

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during the disease course [10–12]. Highly abnormal bone metabolism leads to osteolytic bone lesions and patients experience pain, deformity, neurological damage and loss of mobility [13]. Diagnosis can result in reduction in physical activity (PA), often related to fear of inducing damage to bones that is exacerbated by discouragement from family members and restrictive or inadequate advice from clinical teams [14]. Functional and psychological deficits present at diagnosis are often exacerbated by deconditioning experienced during intensive treatment with chemotherapy and ASCT. Poor physical functioning and perceived loss of mental control are associated with worse psychosocial outcomes and QOL in people undergoing stem cell transplantation [15,16]. Myeloma ASCT recipients have been found to place importance on the role of exercise for enhancing recovery [17–20]. Few studies have evaluated a pre-ASCT exercise in a myeloma-only population, with mixed results [21–24], but studies have demonstrated that it is safe for myeloma patients to exercise whilst undergoing ASCT and may provide physical and psychological benefit at a time in treatment when low PA and deconditioning are evident.

The PERCEPT myeloma trial aimed to investigate the feasibility of a physiotherapist-led exercise intervention as an integral part of the ASCT treatment pathway. Primary objectives related to evaluation of recruitment rate, flow through the study and adherence to the intervention. Secondary objectives were to collect preliminary data on a range of outcomes to inform future trial design.

Materials and methods

The original study protocol [25] and changes to the protocol that were required to continue delivery of the trial remotely during the COVID-19 pandemic [26] have been published. Reporting guidelines for pilot and interventional studies [27,28] have been followed to briefly summarise methods.

Design

A pilot RCT of an exercise prehabilitation and rehabilitation intervention delivered during treatment with ASCT for myeloma.

Ethical approval for the original face-to-face study protocol was granted by London – Camden & Kings Cross Research Ethics Committee (reference 19/LO/0204). A substantial amendment to continue the trial remotely during the pandemic was also given favourable opinion (reference 18/0552 Amendment SA1). The trial was prospectively registered (ISRCTN15875290).

Participants and recruitment

Participants were people with a diagnosis of myeloma, referred to a specialist cancer centre for consideration for ASCT. Participants were approached by the lead author. Written informed consent was obtained from each participant prior to baseline assessment. Randomisation was undertaken using minimisation, with age and gender as the stratification factors. Due to limited staff access to university premises and randomisation software during the pandemic blinding of the lead researcher was not possible.

Intervention and control

Intervention

The exercise intervention (EX) is described in more detail in the published protocols [25,26] and summarised in Table 1. The intervention with incorporated behaviour change techniques was delivered across three phases of ASCT treatment: the prehabilitation phase (from baseline to admission for ASCT); during transplant admission (between hospital admission and discharge from ASCT); and the rehabilitation phase (from hospital discharge to three months post-ASCT).

Control

The control group (CG) was based on usual standard of care provided in the ASCT clinical pathway at the centre. There was no outpatient physiotherapy or rehabilitation service delivered as standard or as part of the clinical pathway for patients with myeloma or those undergoing stem cell transplant at the centre. Those randomised to CG received the usual advice provided by haematology clinical nurse specialists. People undergoing ASCT admitted to the haematology inpatient wards at this centre may receive inpatient physiotherapy or occupational therapy during their admission for mobility or functional concerns related to discharge planning if referred by the medical or nursing teams. This was not withheld for EX or CG participants and was recorded.

Outcomes

Primary outcomes: feasibility

Feasibility outcomes included recruitment rate, reasons for ineligibility or non-participation, attrition, adherence to the intervention and adverse events (AE). Recruitment rate was calculated using the number of potential participants screened as eligible to approach and the number of those who consented to take part and were randomised. Attrition rate was derived by dividing the number of participants withdrawn or lost to follow-up by the number originally randomised. Adherence (attendance of supervised exercise sessions) was recorded by the research physiotherapist and EX participants were provided with paper intervention booklets containing log-sheets. A target recruitment rate of $>50\%$ of potential participants screened as eligible and approached was decided a priori as a primary indication of feasibility and attrition and adherence rates assessed retrospectively for future trial planning [25].

Secondary outcomes

Outcomes were measured at four timepoints: baseline assessment pre-ASCT (T0); on admission for ASCT (T1); on discharge from ASCT admission (T2); and three months post-ASCT (T3). Demographics were self-reported, medical history

Table 1. Exercise intervention summarised according to TIDieR and CERT checklists.

PERCEPT myeloma: prehabilitation and rehabilitation exercise programme during ASCT for myeloma	
Rationale	To evaluate the feasibility of delivering exercise as a component part of the ASCT pathway within myeloma
WHAT: materials	*Intervention materials:* • Intervention booklet (paper) including tasks to facilitate goal setting, identifying barriers/enablers, logsheets to record exercise and information on programme, and BORG scale. *Exercise equipment:* • Resistance bands, multiple grades • Heart rate monitor and watch • Aerobic gym equipment (face-to-face supervised sessions)
WHAT: procedures	The intervention included aerobic and resistance exercise and behaviour change support delivered over three phases: 1. Prehabilitation Phase: from baseline to admission for ASCT; 2. During Transplant Admission: between hospital admission and discharge from ASCT; 3. Rehabilitation Phase: from hospital discharge to three months post-ASCT
WHO: provider	Delivered by physiotherapists with an oncology musculoskeletal background and experience of delivering group based exercise interventions.
HOW: delivery	Group based supervised sessions and home-based individual exercise sessions Phase 1 – Prehabilitation: 1× supervised session (face-to-face or remotely supervised) and 2× unsupervised sessions per week Phase 2 – Admission: remote telephone support Phase 3 – Rehabilitation: ×3 unsupervised sessions with 1× telephone contact to review/progress exercise per week Attendance of supervised sessions was recorded by research team. Adherence to exercise programme was self-recorded by participants in intervention booklets Incorporated behaviour change techniques reported in published protocol [25] *Aerobic exericse:* Gradual cardio progression was achieved by increasing exercise duration by 5 min and intensity by 5% of HRR every week. Resistance exercises: Individually tailored and gradually progressed by the study physiotherapist using 10-repetition maximum assessment, according to published principles [29] *Aerobic exercise:* Treadmill walking or stationary cycling in gym setting; walking, or use of own exercise machine, in home setting. *Resistance exercises:* Multi-joint functional exercises including shoulder press, wall press, seated row, squat, lunge, step ups, bridge, scissors, hip twist. Adverse events were reported by study physiotherapist to chief investigator and recorded on adverse event forms as per local research protocol
WHERE: location	*Original protocol:* Supervised sessions in hospital based gym. Independent sessions at home. *Virtual protocol:* Supervised sessions remotely supervised over video platform Zoom.
WHEN, HOW MUCH: dosage	*Aerobic exercise (Phase 1 and 3):* Frequency 3 times per week Intensity aim 60–80% of HRR (Karvonen formula), Duration starting 15 min, increasing ×5 minutes/week to minimum of 30 min by week 3–4. Increased to 40 min by week 5 pre-ASCT. *Resistance exercise (Phase 1 and 3):* Frequency 3 times per week Intensity determined using 10-repetition max assessment and individually tailored to progress and/or adapt to bone disease. *During phase 2 (transplant admission):* All exercise was highly individualised according to symptoms and ability to participate in exercise programme.
TAILORING: what, how	All exercise was individually tailored according to ability, presence of myeloma related bone disease, and individual symptoms and published principles [29].

ASCT: autologous stem cell transplant; CERT: consensus on exercise reporting template; HRR: heart rate reserve; TIDieR: template for intervention description and replication.

and ASCT admission data were recorded from electronic hospital records.

Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy (FACIT-F) questionnaire [30] and QOL was assessed using the European Organisation for Research and Treatment of Cancer QOL Questionnaire (EORTC QLQ-C30) [31], the Functional Assessment of Cancer Therapy Bone Marrow Transplantation (FACT-BMT) scale questionnaire [32] and the EuroQol EQ-5D-5L Questionnaire [33].

Functional capacity was assessed using the six-minute walk test (6MWT), hand-grip strength (HGS) and timed sit-to-stand test (TSTS). Predicted 6MWT distance were calculated using a reference equation [34] and baseline scores were calculated as percentage of predicted score. PA and sedentary time were measured objectively using accelerometer (activPAL) and self-reported questionnaire (International Physical Activity Questionnaire – short form (IPAQ-SF) [35]). The activPAL was attached to the midline anterior thigh using waterproof dressing with instruction to wear continuously for seven days.

Originally, all assessments were conducted in person in the clinic or hospital setting. Following adaptation to virtual delivery, 6MWT and HGS measures of functional capacity were discontinued and participants were requested to complete a baseline TSTS remotely-supervised by the physiotherapist over Zoom and requested to conduct a self-assessed TSTS at follow-up timepoints, reporting their repetitions on the postal questionnaire pack. Objective PA measurement using accelerometer was captured for baseline only and participants self-attached the device with remote supervision. All patient reported outcome measures (PROMs) continued *via* postal return [26].

Statistical analysis

Primary outcomes of trial feasibility are reported as frequencies and proportions. Data collected for the questionnaire-based secondary measures were more complete and changes to these measures over time were explored using linear mixed-effect models (LMEM) for repeated measures. Models included allocation × timepoint as fixed effects and participants as random effect. As age and gender were stratified for during randomisation they were not included within the model as covariates. Pandemic effects on ASCT services led to variability in time between baseline (T0) and timepoint 1 (T1), therefore time between baseline and ASCT was included in the model as a covariate. The LMEM model used maximum likelihood estimation to produce group mean estimates and within-group and between-group differences for each timepoint, with 95% confidence intervals (95% CI). Changes to secondary outcomes of functional capacity and objective PA resulted in very small numbers for each measure especially at follow-up timepoints, therefore these measures are presented descriptively. Due to the feasibility study design, sample size constraints and underpowering, significance (p-value) has not been reported but trends in the data are highlighted. Data were analysed using statistical software Jamovi [36].

Results

Primary outcome: feasibility

Recruitment took place between June 2019 and October 2020, with a six month pause in recruitment between March and August 2020 due to the COVID-19 pandemic. Recruitment stopped early due to further disruption to the ASCT pathway with the second wave of the pandemic in October 2020. Over 11 months, 123 patients were identified and screened for eligibility, of whom 109 (89%) were eligible and approached. Of these, 50 (46%) consented and were randomised (27 CG; 23 EX). Reasons for ineligibility and declining participation, according to original and virtual protocol, are presented in Figure 1. Baseline demographics and disease characteristics by group allocation were similar for all parameters except education levels (Table 2). The study sample was 62% ($n = 31$) male, with a mean age of 60.4 years (SD = 9, range 37–72).

33 out of 50 (66%) participants completed an assessment at the final timepoint. 20% ($n = 10$) participants were withdrawn due to not proceeding to ASCT because of progression of disease or other clinical decision. Five (10%) participants were lost to follow-up and two (4%) participants died. Of the 39 who proceeded to ASCT (23 CG; 16 EX), median time from baseline assessment to transplant (day '0') was 83 days (range 14–436) with huge variation due to delays caused by the pandemic. Transplant admission characteristics for each group are presented in Table 3. Both groups had similar overall transplant admission and ambulatory-care length of stay. All EX participants commenced their admission in ambulatory care and 25% ($n = 4$) remained in ambulatory care for their whole ASCT admission, compared to 13% ($n = 3$) of CG. In the approximate three-month period following ASCT, 26% ($n = 6$) of CG were readmitted to hospital compared to 19% ($n = 3$) of EX.

Prior to the pandemic, median time to receive the pre-ASCT prehabilitation was 7.5 weeks (range 5–15) and median attendance to face-to-face supervised exercise sessions was 3.5 sessions (range (0–5). Following amendment to the virtual protocol, the median number of weeks to receive pre-ASCT prehabilitation was 8.5 weeks (range 1–33) and median attendance to remotely supervised exercise sessions was 3.5 sessions (range 0–27), with large variation due to delays to ASCT delivery. In the rehabilitation phase, post-ASCT, participants had median 8 (range 0–11) telephone contacts from the physiotherapist. Return of intervention logbooks was poor. 26% (6/23) participants returned a prehabilitation pre-ASCT logbook. 25% (4/16) participants who were admitted for ASCT returned an admission logbook. 38% (6/16) participants returned a rehabilitation post-ASCT logbook. In total only three participants (19%) returned a logbook for all three phases.

There were two AEs during the trial, one in each study arm. One CG participant was found to have a new spinal fracture at the site of a previously healed fracture on routine imaging pre-ASCT. This AE was not related to taking part in the study. One EX participant reported a mild episode of dizziness during a face-to-face supervised exercise session, which may have been related to the intervention.

Secondary outcomes

Mean estimates per group at each timepoint, along with within- and between-group changes for fatigue and QOL are presented in Supplementary Tables 1 and 2. Notable within-

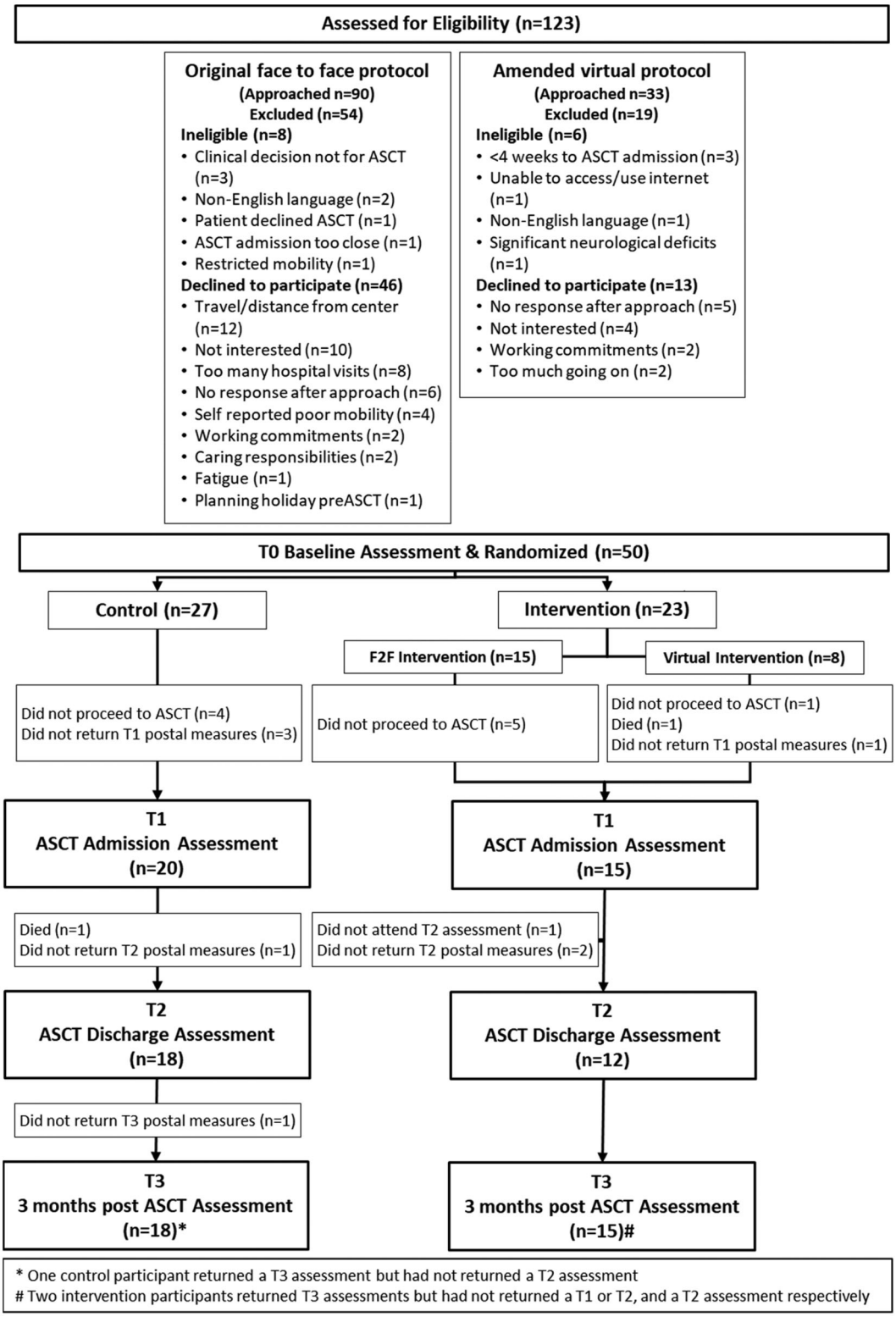

Figure 1. CONSORT diagram of participant flow through study and reasons for exclusion.

group improvements beyond meaningful important difference (MID) in the prehabilitation phase (T0–T1) were evident in the EX for fatigue (FACIT-F) [37,38] (EX: +5.7, 95%CI 0.1, 11.2; CG: +3.3, 95%CI −1.5, +8.1) and QOL measured by FACT-G [39] (EX: +8.4, 95%CI 1.9, 14.8; CG: +4, 95%CI −1.5, +9.5) and FACT-BMT [32] (EX: +10.3, 95%CI 2.1,+18.5; CG: +4.1, 95%CI −2.9, +11.1), but not in the CG. QOL scores for both groups deteriorated during admission for ASCT before improving in the rehabilitation phase (T2–T3).

Descriptive data for functional capacity outcomes and PA are presented in Supplementary Table 3–6. Follow-up data were limited for functional capacity measures due to protocol changes in response to the pandemic. The median percentage of predicted 6MWT value for $n = 36$ participants at

Table 2. Baseline demographics by group.

	Control ($n = 27$)	Intervention ($n = 23$)
Age, years		
mean ± SD	61.3 ± 8.7	59.3 ± 9.4
range	40–72	37–72
<65 *n* (%)	15 (56)	16 (70)
≥65 *n* (%)	12 (44)	7 (30)
Sex, *n* (%)		
Male	18 (67)	13 (57)
Female	9 (33)	10 (43)
Weight (kg), mean ± SD	78.6 ± 16.0	84.1 ± 14.9
Body mass index (BMI) (kg/m^2), mean ± SD	26.9 ± 4.4	29.7 ± 4.5
BMI status, *n*(%)		
Underweight	1 (4)	–
Healthy weight	10 (37)	3 (13)
Overweight	10 (37)	11 (48)
Obesity	6 (22)	9 (39)
Self-assigned ethnicity, *n* (%)		
White	21 (78)	16 (70)
Black or Black British	6 (22)	4 (17)
Asian or Asian British	–	1 (4)
Other	–	2 (9)
Marital status, *n* (%)		
Married, civil partnership or cohabiting	21 (78)	17 (74)
Single	2 (7)	4 (17)
Separated, divorced/civil partnership dissolved	1 (4)	1 (4)
Widowed	3 (11)	–
Rather not say	–	1 (4)
Social situation, *n* (%)		
Lives with spouse/partner only	13 (48)	8 (35)
Lives with immediate family (incl children)	7 (26)	13 (57)
Lives alone	7 (26)	2 (9)
Education, *n* (%)		
Higher (Level 6 degree education or greater)	16 (59)	6 (26)
Lower (Level 5 or less)	10 (37)	15 (65)
Missing	1 (4)	2 (9)
Employment status, *n* (%)		
Retired	10 (37)	8 (35)
On temporary or sick leave	7 (26)	7 (30)
Working full time	5 (19)	3 (13)
Working part time	4 (15)	4 (17)
Unemployed	1 (4)	1 (4)
Time from diagnosis or relapse to baseline, months		
median (IQR)	6 (5,10)	7 (6,11)
range	3–12	4–82
IMWG Frailty Assessment Score, *n*(%)		
Fit	22 (81)	18 (78)
Intermediate fit	5 (19)	3 (13)
Frail	–	2 (9)
Previous ASCT, *n*(%)	5 (19)	4 (17)
Bone disease, *n*(%)	20 (74)	18 (78)
Axial disease	15 (56)	11 (48)
Axial and peripheral disease	5 (19)	7 (30)
No bone disease	7 (26)	5 (22)
Required spinal brace, *n*(%)	9 (33)	9 (39)
Previous radiotherapy, *n*(%)	3 (11)	4 (17)
Previous surgery for myeloma disease, *n*(%)	2 (7)	3 (13)
Kyphoplasty	–	2 (9)
Vertebroplasty	1 (4)	–
Other	1 (4)	1 (4)
Ongoing symptoms of bone disease at baseline, *n*(%)		
Disease related pain	13 (48)	12 (52)
Restricted mobility	1 (4)	3 (13)
None/asymptomatic	9 (3)	6 (26)
Non myeloma related pain	4 (15)	2 (9)

T0 was 79% (IQR 60.1, 84.9) and 19 (53%) had a baseline 6MWT score lower than 80% of their predicted value indicating reduced functional capacity [40]. Greater improvements in median 6MWT distance were seen in the EX in the prehabilitation phase and over the length of the study. Data from a subgroup analysis of $n = 11$ participants who completed a 6MWT at all timepoints indicated a trend for MID improvement in median 6MWT distance over the length of the study for the EX, with less deterioration during ASCT admission compared to CG, who had a MID deterioration over the length of the study. There were no meaningful changes to hand-grip strength.

TSTS protocol was changed from a 30 second protocol to 1 minute protocol on adaptation for remote delivery [26].

Table 3. Transplant admission characteristics by group.

	Control ($n = 23$)	Intervention ($n = 16$)
Time baseline to ASCT D0, days		
Mean ± SD	128.4 ± 102.6	138.3 ± 117.2
Median (IQR)	83.0(56.5,184.5)	74.5 (54.8,241.3)
Range	21–436	14–385
Transplant admission total LOS, days		
Mean ± SD	17.0 ± 2.4	17.0 ± 3.4
Median (IQR)	16 (16,18)	16 (15,17)
Range	14–25	14–26
Died during admission (*n*)	1	–
Started admission in ambulatory-care, *n* (%)	20 (87)	16 (100)
Remained in ambulatory-care for whole admission, *n* (%)	3 (13)	4 (25)
Not admitted to ambi-care	3 (13)	–
Length of stay in ambulatory-care, days		
Mean ± SD	9.9 ± 3.8	9.5 ± 3.8
Median (IQR)	9 (8,10)	8 (7,11)
Range	4–18	3–17
Not admitted to ambulatory-care (*n*)	3	–
Readmitted to hospital within 3/12 post ASCT, *n* (%)	6 (26)	3 (19)
Died during admission	1 (4)	–
AHP referral during admission, *n* (%)		
Physiotherapy	8 (34)	6 (38)
Number of contacts, median (range)	1 (0–8)	1.5 (0–4)
Number of contacts, mean ± SD	2.1 ± 2.8	1.8 ± 1.5
Occupational therapy	4 (17)	1 (6)
Dietetics	9 (39)	10 (63)

TSTS data indicates greater within-group improvements for the EX in the prehabilitation phase (T0–T1), the rehabilitation phase (T2–T3) and over the length of the study (T0–T3). However, this data is limited by very small numbers at follow-up timepoints.

Both groups self-reported similar levels of PA (IPAQ-SF) at T0 but the EX reported higher levels of total PA at T1 (EX: median 2910 MET.mins/week [IQR 1138.5, 4172]; CG: 1512 MET.mins/week [639, 2094.8]) and T3 (EX: median 2259 MET.mins/week [IQR 887.3, 3877.5]; CG: 924 MET.mins/week [678, 2430]). At T0 22% of participants self-reported activity levels that met recommendations for aerobic PA. At T3, three months post-ASCT, 32% self-reported sufficient activity. There was a small difference in the number meeting guidelines at T0 in the EX (EX: 26%; CG: 19%). There was no change in the proportion of CG meeting guidelines in the week prior to ASCT admission (T1) whereas there was a small increase in the EX (EX: +7%; CG: +1%). At T3, more EX participants reported PA in line with recommended levels (EX: 40%; CG: 25%). Across the length of the study (T0–T3) the proportion of those meeting PA guidelines rose by 14% in the EX compared to 6% in the CG. Analysis of objective PA data was limited by low sample size, but patterns of promise were seen with the EX increasing PA, whereas the CG became less active over the course of the study.

Discussion

Feasibility

This pilot RCT aimed to investigate the feasibility of a physiotherapist-led exercise intervention as an integral part of the ASCT treatment pathway in myeloma. The COVID-19 pandemic resulted in significant disruption and necessitated major amendment to the study design [26]. Despite recommencing recruitment virtually with good uptake, the pandemic further disrupted the ASCT pathway at our centre [41] and therefore recruitment ended earlier than intended. The overall recruitment rate was lower than the a priori target for feasibility of >50% and lower than those reported by other trials of exercise interventions during stem cell transplant (reporting uptake of 63–68%) [42,43] and those from non-ASCT myeloma samples (reported uptake 75–80%) [44,45]. None of the forementioned studies were conducted in the UK and there may be different geographical factors at play when accessing specialist centres for trials. A single arm feasibility study of a prehabilitation intervention delivered prior to ASCT in myeloma conducted in the UK reported a lower recruitment rate of 41%, with most eligible participants declining participation due to travel required to study venue, which is in line with our findings [24].

Attrition rate of 34% for the trial is in line with other exercise studies in myeloma [21,22, 24, 45,46]. The main reason for attrition was related to not proceeding to undergo ASCT and therefore most participants were lost prior to first follow-up assessment. Dropout for other reasons was low with high study completion rate among those who underwent ASCT (85%). A strength of the original protocol was alignment of study assessments with usual care appointments which resulted in better data completion during face-to-face attendances pre-pandemic. The greater proportion lost to follow-up in the virtual protocol may have been due to reliance on postal return for study assessments required during the pandemic.

Safety and adherence

Another positive outcome was the low occurrence of AE, with no serious AE occurring. The occurrence of a new spinal fracture in the CG highlights the fragility of the study population and the continued need for close monitoring and individualised tailoring of exercise among people with myeloma.

The incidence of myeloma-related bone disease and previous skeletal events in our sample is representative and similar levels of bone disease have been reported in more recent myeloma studies, building the case for safety of appropriately tailored exercise for these patients [45, 47].

Overall, data for the supervised sessions in the prehabilitation phase of the intervention shows variable length of time available to receive input with low median attendance. The pandemic influenced the variability in this data with both weeks available and number of weeks attended ranging widely as some participants had their ASCT postponed due to subsequent waves of the pandemic [41]. Attendance of exercise sessions is only one measure used to describe adherence in exercise trials, and should be considered alongside measurement of completion rates of the exercise prescribed [48]. Deeper investigation of adherence to the exercise programme as prescribed was not possible due to poor return of paper-based intervention booklets.

PROMS and functional outcomes

Some secondary outcomes indicate promise for exercise before, during and after ASCT in myeloma. This trial is novel for capturing outcomes on admission and day of discharge from ASCT admission therefore capturing the notable deterioration in QOL and levels of fatigue associated with undergoing ASCT [49,50]. Baseline PROMs scores for the sample were comparable to other pre-ASCT myeloma samples [50]. PROMs demonstrated similar trajectories of change between timepoints for both trial groups. There were promising indications of intervention effects on these outcomes, particularly in the prehabilitation phase, with several outcomes indicating change in scores beyond MID in the EX.

Secondary outcomes related to functional capacity and PA were also limited by adaptation of study protocols and although these results should be interpreted with caution due to small sample sizes at follow-up, they do indicate promising signals. The descriptive analysis of all 6MWT data and the subgroup analysis of the eleven complete datasets indicate similar patterns of change. The improvement in the pre-ASCT phase of our trial was more modest than that reported by Mawson et al. (2021), who described a mean change of 104.9 m (SD 71.4) in their pre-post assessment of myeloma patients who underwent a six-week exercise prehabilitation intervention pre-ASCT [24]. Over the length of our trial the EX improved beyond MID, to result in better functional capacity at three months post-ASCT, whereas the CG worsened. The deterioration in CG was equivalent to a 0.09 metres per second (m/s) reduction pre- to post-ASCT. A 1-m/s reduction in walking speed is associated with a 20% increase in mortality (HR 1.20; 95%CI 1.12, 1.29; $p<.0001$) and a 33% increase in unplanned hospital admissions (OR 1.33; 95%CI 1.16, 1.51) in older people with haematological cancer [51] and may be clinically important. Median 6MWT distance for the CG at 3 months post-ASCT is also in line with those reported in a cross-sectional study of myeloma patients who were on average 17 months post-ASCT [52]. These patterns and similarities with other studies, albeit to be interpreted with caution due to limitations of the data, may contribute towards refuting the notion that people with myeloma naturally return to baseline or expected functional abilities with time post-ASCT and indicates that prehabilitation and rehabilitation programs may be valuable.

Physical activity

The continued administration of the self-reported IPAQ-SF questionnaire did allow for more complete data regarding PA behaviour. Baseline total PA was similar for both groups and in line with those reported among myeloma patients recruited by Mawson et al. [24]. The proportion of participants in this trial active to levels in line with PA guidelines for aerobic PA is higher than previously reported among myeloma patients [53–55]. Comparably, the proportions meeting guidelines at baseline in this trial indicate that the sample may have been more active than pre-ASCT myeloma patients described previously, however research participants are known to overestimate levels of PA in self-report questionnaires [56].

Considerations for future research

Improvement of fatigue, QOL, functional capacity and PA prior to transplant and its maintenance during admission may be an important factor not only in optimising physical and mental wellbeing but may also facilitate timely discharge from hospital and early initiation of restorative rehabilitation following treatment [57]. The potential benefits of physiotherapist-led exercise before, during and after ASCT for myeloma warrant further investigation in future studies with adequate sample size.

A strength of this trial was its pragmatic design mapped to and embedded within an existing clinical pathway at a large UK centre but it is not without limitations. Although rapid adaptation of the original protocol to a virtually-delivered one allowed for continued recruitment and data capture during the uncertainty of the pandemic, a reliance on postal delivery to return study assessments and intervention logbooks, self-assessment of follow-up functional measures and further disruption to ASCT clinical services, resulted in large variation in some feasibility outcomes and missing data for follow-up secondary outcomes.

Overall, results indicate feasibility of the pilot trial in relation to recruitment rate, attrition, and acceptability of the intervention. However, a number of process-related deficits became evident that undermined thorough evaluation of the intervention. Some participants received input from physiotherapists during their ASCT admission on the inpatient hospital ward as part of usual care. The number of referrals and input was similar in both arms and is not likely to have influenced results. Two qualitative studies were carried out alongside the trial; one among study completers did indicate probable contamination of CG, with some participants reporting seeking exercise support outside of the study in the pre- and post-ASCT phases [58]. Despite the disruption of the pandemic, rapid adaptation of the trial allowed

continuation of recruitment and opportunity to investigate feasibility of both face-to-face and virtually delivered research. The second related qualitative study explored the views of those who declined the trial and travel required for the face-to-face protocol was a key consideration for non-participation [59]. Virtually recruited studies have been found to recruit more geographically spread participants, at a faster rate to traditionally recruited studies [60] and so given the uncertainty due to the pandemic, future work should aim to better quantify recruitment and eligibility rates for a virtually delivered study during a typical ASCT clinical pathway. It is likely that a hybrid approach, using key clinical touch points to undertake face-to-face study assessments, with use of a remotely-delivered intervention to improve access, supported by digital resources to support exercise delivery and automate data capture related to adherence, may offer the best approach.

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ORCID

Orla McCourt http://orcid.org/0000-0001-7572-2540
Kwee Yong http://orcid.org/0000-0002-6487-276X

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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